REMARKS

The Official Action dated December 18, 2008 has been carefully considered. Accordingly, the present Amendment is believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, the Title of the application is amended to reflect the title set forth on the English language translation of the specification filed upon entry into the U.S. National Stage. Additionally, the specification is amended to set forth the 371 status. Claims 1, 7 and 16-20 are cancelled and new claims 21 and 22 are presented. Claim 21 contains limitations from elected claim 20, from claims 17 and 18, and from the specification, for example at page 6, lines 9-27, page 8, line 16-page 9, line 2, page 9, lines 6-10, page 13, line 19, and page 20, lines 6-10. Support for claim 22 may be found at page 34, lines 14-24 of the specification. Withdrawn claims 2-6 and 8-15 are amended to recite methods and to depend, directly or indirectly, from claim 21. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

Claims 1-19 were previously withdrawn as directed to nonelected inventions. As claims 2-6 and 8-15 now recite methods and depend directly or indirectly from claim 21, examination of claims 2-6 and 8-15 with claim 21 is requested. Otherwise, rejoinder of claims 2-6 and 8-15 upon allowance of claim 21 is requested.

In the Official Action, claim 20 was rejected under 35 U.S.C. §112, second paragraph, as being indefinite. First, the Examiner objected to the term "substantially" in claim 20 as being a relative term. The Examiner also objected to the term "without being administered through a systemic blood flow" as unclear and not allowing one of skill in the art to ascertain the metes and bounds of the claims. The Examiner also asserted that it is unclear what ocular conditions are being treated as the claims encompass all ocular conditions but not all ocular

diseases are treatable. The Examiner cited the Moss and Newman publications as disclosing Leber's congenital amaurosis and Leber's hereditary object neuropathy as ocular diseases which are not treatable.

These rejections are traversed with respect to claim 21, and reconsideration is respectfully requested. First, Applicants note that the term "substantially" is omitted from claim 21, and, additionally, claim 21 recites the amount of remedy transferred by percutaneous permeation within 8 hours after application is at least twice that transferred by systemic blood flow. The phrase "without being administered through a systematic blood flow" has been omitted from claim 21. Finally, the method of claim 21 is for transferring a remedy for ophthalmic disease selected from a recited group, therefore omitting diseases for which there is no known remedy. Accordingly, claim 21 is believed to be definite and the rejection under 35 U.S.C. §112, second paragraph, has been overcome.

Claim 20 was rejected under 35 U.S.C. §102(b) as being anticipated by the Tojo et al PCT Publication WO 01/26648 and its corresponding U.S. Patent No. 7,052,714. The Examiner asserted that Tojo et al teach transdermal preparations comprising an adhesive with a drug, a release membrane and a lining film support and that the patch can be applied to any desired body surface including the eyelid.

However, Applicants submit that claim 21 is not anticipated by, and is patentably distinguishable from Tojo et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, the present invention is directed to a method for transferring a remedy for ophthalmic disease selected from the group consisting of ocular infection, allergic conjunctivitis, pollinosis and vernal conjunctivitis to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea. The method comprises applying a pressure-sensitive adhesive tape preparation comprising a plaster layer provided

on a support, to a front skin surface of an upper eyelid and/or a lower eyelid to transfer the remedy for ophthalmic disease in the plaster layer to the external ophthalmic tissue by percutaneous permeation in such a manner that the remedy for ophthalmic disease is transferred by percutaneous permeation to the external ophthalmic tissue from the skin surface. The plaster layer contains the remedy for ophthalmic disease and a pressure-sensitive adhesive. The amount, in units of μg/g·tissue, of the remedy transferred by percutaneous permeation to the external ophthalmic tissue by the application within 8 hours after the application amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow.

Tojo et al is cited at page 4 of the present application and is directed to an ophthalmic transdermal patch for treating diseases of the posterior segment of the eye, i.e., the lens, the vitreous body, the choroids and the retina (see, for example, column 1, lines 6-9). Tojo et al teach that their patch delivers drug to blood plasma which in turn delivers the drug to the posterior segment of the eye (see the in vivo test results at columns 12-13). In contrast, the method of claim 21 is directed to transferring a remedy to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea, and employs percutaneous permeation for drug delivery rather than the systemic blood flow employed by Tojo et al.

More specifically, according to Tojo et al, after the drug is caused to be percutaneously absorbed, the drug is transferred into the blood to administer the drug to the posterior segment of the eye from the plasma in the blood through the systemic blood flow. For example, the Tojo et al test results examine both the plasma concentration and posterior eye concentration of active ingredient. Specifically, Tojo et al indicate that the prednisolone amount was determined in the plasma and the eyeball of the rats to which were applied a 3% prednisolone-containing preparation, P5 and, as a result, 70 ng/g prednisolone was detected 6 hours after the application of the preparation, indicating that prednisolone was transferred to

the interior of the eye at a concentration that was equivalent to 18% of the plasma concentration (Table 8, column 12, line 64-column 13, line 7). Additionally, Tojo et al disclose in Table 8 that 7.2 ng/g of SJA601 7 was detected in the eyeball 12 hours after the application of the SJA6017-containing preparation, reaching about 16% of the plasma concentration of the drug, which is higher than the corresponding value (13%) detected after intravenous application. Tojo et al conclude that this shows the continuous nature of absorption of SJA6017 from the patch and that this method of administration of a drug by transdermal patches is a method available to continuously transfer a drug from the plasma into the eyeball (column 13, lines 39-48).

These teachings of Tojo et al clearly show that in the Tojo et al method, after the drug is percutaneously absorbed, the drug is transferred into the blood to administer the drug to the posterior segment of the eye from the plasma in the blood through the systemic blood flow. On the other hand, the method of claim 21 is directed to transferring a remedy to external ophthalmic tissue primarily by percutaneous permeation, i.e., the amount, in units of μg/g·tissue, of the remedy transferred by percutaneous permeation to the external ophthalmic tissue (conjunctiva, lacrimal tissue and cornea) by the application within 8 hours after the application amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow. Further, as shown in the examples of the present specification, the amount of remedy transferred according to the method of claim 21 is greater than that achieved either through plasma distribution or through application of eye drops or the like. See, for example, Table 1 at page 38 and Table 4 at page 43 of the present specification. Tojo et al do not teach such a method or recognize the improvement thereof in treating an external ophthalmic tissue as presently claimed.

In fact, in their Background Art discussion, Tojo et al teach that with administration of a drug in the form of eye drops or by subconjunctival injection, the concentration of the

drug generally reaches therapeutically effective levels in the anterior segment of the eye, including the cornea and the anterior aqueous humor, but, in tissues in the posterior segment of the eye, including the lens, the vitreous humor, the choroid and the retina, which are located in deeper sites of the eye, the concentration of a drug generally would hardly, or almost never, reach therapeutically effective levels after its topical application either in the form of eye drops or by subconjunctival injection (column 1, lines 16-26). Thus, Tojo et al teach that eye drops or subconjunctival injection are suitable application techniques for delivering an active agent to the anterior segment of the eye, but other techniques are necessary for delivery of an active agent to posterior segments of the eye. By teaching that eye drops or subconjunctival injection are suitable application techniques for the anterior segment of the eye, Tojo et al teach away from the use of percutaneous adsorption for treatment of the anterior segment of the eye.

Tojo et al teach their ophthalmic transdermal patch may be applied at any location of the body surface as desired, including a site relatively close to the eye, e.g., on the temple or around the eye, in particular on the skin of the eyelids or next to the lateral angle of the eye (column 7, lines 35-40). On the other hand, the method of claim 21 requires that the pressure-sensitive adhesive tape preparation is applied to a front skin surface of an upper eyelid and/or a lower eyelid to transfer the remedy by percutaneous permeation to the external ophthalmic tissue. Thus, Tojo et al are concerned with delivery of the drug to the blood, not to external ophthalmic tissue.

The present methods of transferring a remedy from the pressure-sensitive adhesive tape preparation to the external ophthalmic tissue including the conjunctiva, lacrimal tissue and cornea by percutaneous permeation have various advantages. Efficacy of the remedy for ophthalmic disease is achieved faster as the percutaneous permeation delivers the remedy to the external ophthalmic tissue of the eye faster than it would be delivered through systemic

blood flow. Additionally, as a higher amount of the applied drug is delivered to the external ophthalmic tissue by percutaneous permeation as compared with delivery through systemic blood flow, even a drug low in percutaneous permeability can be administered in an amount sufficient to provide efficacy. Further, even when the remedy is a drug having skin irritability, efficacy and a reduction of skin irritability can be reconciled by controlling percutaneous absorbability and the amount permeating the skin. Finally, problems with systemic drug delivery, including undesirable side effects, can be reduced or eliminated, and the efficacy of the remedy can be sustained over a long period of time. These advantages are demonstrated in the Examples in the present specification.

Anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference, *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999). As Tojo et al teach methods for treating diseases in the posterior segment of the eye by systemic blood flow delivery of a drug and teach that eye drops or subconjunctival injection techniques are adequate for drug delivery to the anterior segment of the eye, and Tojo et al do not teach a method for transferring a remedy for ophthalmic disease selected from the group consisting of ocular infection, allergic conjunctivitis, pollinosis and vernal conjunctivitis to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea, Tojo et al do not describe each and every element of the present claim 21 and therefore do not anticipate claim 21. The rejection under 35 U.S.C. §102(b) is therefore overcome. Reconsideration is respectfully requested.

Claim 20 was also rejected under 35 U.S.C. §103(a) as being unpatentable over the Kissel et al U.S. Patent No. 5,593,686 in view of the Trimming et al U.S. Patent Publication No. 2001/0006968 and in view of the Lerner et al PCT Publication WO 97/18855. The Examiner asserted that Kissel et al teach a transdermal patch with a reservoir and a support

for administration of active agents including ketotifen. The Examiner relied on Trimming et al as teaching ketotifen for treatment of allergic conjunctivitis and on Lerner et al as teaching the skin of the eyelid has a resistance lower than that on the rest of the skin surface, and concluded it would have been obvious to apply the ketotifen patch of Kissel et al on the eyelid in view of Trimming et al and Lerner et al.

However, Applicants submit that claim 20 is not rendered obvious over, and is patentably distinguishable from, the combination of Kissel et al, Trimming et al and Lerner et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, as discussed in detail above, the present invention is directed to a method for transferring a remedy for ophthalmic disease selected from the group consisting of ocular infection, allergic conjunctivitis, pollinosis and vernal conjunctivitis to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea. The method comprises applying a pressure-sensitive adhesive tape preparation comprising a plaster layer provided on a support, to a front skin surface of an upper eyelid and/or a lower eyelid to transfer the remedy for ophthalmic disease in the plaster layer to the external ophthalmic tissue by percutaneous permeation in such a manner that the remedy for ophthalmic disease is transferred by percutaneous permeation to the external ophthalmic tissue from the skin surface. The plaster layer contains the remedy for ophthalmic disease and a pressure-sensitive adhesive. The amount, in units of μg/g·tissue, of the remedy transferred by percutaneous permeation to the external ophthalmic tissue by the application within 8 hours after the application amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow.

Kissel et al disclose various embodiments of pharmaceutical compositions for the transdermal systemic administration of an active agent (Abstract). In one embodiment, the active agent may comprise ketotifen. Kissel et al disclose that the pharmaceutical

compositions may be applied to intact skin, e.g. on the chest, back, arm or behind the ear, of a subject and the penetration of the active agent may be followed by measuring the amount of active agent in the blood (column 5, lines 40-44).

Thus, while the present invention is directed to transferring a remedy for ophthalmic disease to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea, Kissel et al disclose a method for systemic administration of a drug, i.e., through blood flow. As the Examiner noted, Kissel et al do not teach placing a composition on the eyelid. More importantly, however, Applicants find no teaching or suggestion by Kissel et al regarding any method for transferring a remedy to an external ophthalmic tissue, particularly by percutaneous permeation to the external ophthalmic tissue, and specifcally wherein the amount, in units of μg/g·tissue, of the remedy transferred by percutaneous permeation within 8 hours after the application amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow.

The deficiencies of Kissel et al are not resolved by Trimming et al or Lerner et al. That is, Trimming et al teach an ophthalmic composition, for example, eye drops, comprising ketotifen for treatment of allergic conjunctivitis is compatible with soft contact lens (paragraph [0003]). Thus, while Kissel et al are directed to systemic administration compositions, Trimming et al are directed to eye drops. One of ordinary skill in the art would have no reason to combine any of the systemic administration composition teachings of Kissel et al with the eye drops of Trimming et al as these two references relate to different administration routes and mechanisms and neither reference teaches, suggests or recognizes that application of a pressure-sensitive adhesive tape preparation to a front skin surface of an upper eyelid and/or a lower eyelid as presently claimed transfers a remedy for ophthalmic disease to an external ophthalmic tissue by percutaneous permeation.

Finally, Lerner et al disclose an iontophoresis device for enhancing the delivery of a drug into a selected organ or tissue, for example the brain, which device includes special electrodes connected with a selected energy source which maintains an energy field before and during the delivery of the drug. Beginning at page 37, line 34, Lerner et al disclose an embodiment for intracerebral transocularis wherein iontophoresis is conducted through the eyeballs. As noted by the Examiner, Lerner et al disclose that skin of the eyelid has a resistance lower than that on the rest of the skin surface and a resistance of the cornea and of the sclera is negligible. It is apparent that Lerner et al are referring to resistance to the flow of current, as Lerner et al further indicate that in this method, a split active electrode must be placed over the eyes and is covered by cotton or other material wetted in the solution of the necessary active substance and touching the skin as the electrodes themselves must not touch the skin, another split electrode covered by cotton or other material and wetted in the water is fixed on the mastoid processors or on another place or a single passive electrode is fixed on the back of the head in the area of cervical vertebrae or on another place, and, depending on individual tolerance (pressure or some other unpleasant feelings), current intensity can increase up to 10 mA (page 38, lines 2-18).

Thus, Lerner et al are concerned with administration of a drug to the brain by bypassing the blood-brain barrier using iontophoresis. One of ordinary skill in the art would have had no apparent reason to combine any of the teachings of Lerner et al with either the systemic administration compositions of Kissel et al or the eye drops of Trimming et al. Lerner et al's teaching of the resistance of the eyelids to the flow of current is simply irrelevant to Kissel et al's systemic administration compositions and Trimming et al's eye drops.

In determining patentability under 35 U.S.C. §103, it is necessary to determine whether there was an apparent reason to combine the known elements of the prior art in the

fashion of the claims at issue, *KSR International Co. v. Teleflex, Inc.*, 550 US 398, 418 (2007). As Kissel et al, Trimming et al and Lerner et al are all directed to different and distinct modes of administration of actives, and none of these references provide any teaching of a method for transferring a remedy to an external ophthalmic tissue by percutaneous permeation to the external ophthalmic tissue, these references cannot be properly combined to result in the method of claim 21. Accordingly, combination of these references does not render the present method of claim 21 obvious, and the rejection under 35 U.S.C. §103 is therefore overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Official Action, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Finally, claim 20 was provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 3-7, 11, 23 and 25-27 of copending application Serial No. 10/569,772 in view of Tojo et al. This rejection is traversed and reconsideration is respectfully requested.

Present claim 21 is directed to a method for transferring a remedy for ophthalmic disease selected from the group consisting of ocular infection, allergic conjunctivitis, pollinosis and vernal conjunctivitis to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea. The claims of copending application Serial No. methods of promoting lacrimal fluid secretion. Applicants submit that the respective methods are distinct and nonobvious over one another, whereby the rejection should be withdrawn. Reconsideration is respectfully requested. Moreover, in the event that the Examiner is of the opinion that the double patenting rejection should be maintained and this provisional double patenting rejection is the only rejection remaining in the present

application, the examiner should withdraw the rejection in the present application and permit the present application to issue as a patent, MPEP §804.

It is believed that the above represents a complete response to Official Action, and places the present application in condition for allowance. In the event there are any outstanding issues relating to this application, the Examiner is urged to telephone the undersigned to efficiently resolve the same. Reconsideration and an early allowance are requested.

Please charge any fees required in connection with the present communication, or credit any overpayment, to Deposit Account No. 503915.

Respectfully submitted,

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